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hydrochloride, chlorambucil, cyclophosphamide, diethyl sulfate, acrylamide monomer, triethylene melamin (TEM), melphalan, nitrogen mustard, vincristine, dimethylnitrosamine, N-methyl-N'-nitro-Nitrosoguanidine (MNNG), 7,12 dimethylbenz (a) anthracene (DMBA), ethylene oxide, hexamethylphosphoramide, bisulfan. In a preferred aspect of the invention, a mutagenesis technique is employed that confers a mutation rate in the range of 1 mutation out of every 100 genes to 1 mutation per 1,000 genes. The use of such combination (MMR deficiency and externally applied mutagen) permits the generation of a wide array of genome alterations (such as, but not limited to, expansions or deletions of DNA segments within the context of a gene's coding region, a gene's intronic regions, or 5' or 3' proximal and/or distal regions, point mutations, altered repetitive sequences) that are preferentially induced by each particular agent.

Mutations can be detected by analyzing for alterations in the genotype of the cells or animals, for example by examining the sequence of genomic DNA, cDNA, messenger RNA, or amino acids associated with the gene of interest. Mutations can also be detected by screening/observing the phenotype of the gene. An altered phenotype can be detected by identifying alterations in electrophoretic mobility, spectroscopic properties, or other physical or structural characteristics of a protein encoded by a mutant gene. One can also screen for altered function of the protein *in situ*, in isolated form, or in model systems. One can screen for alteration of any property of the cell or animal associated with the function of the gene of interest, such as, but not limited to, measuring protein secretion, chemical-resistance, pathogen resistance, etc.

Inducible vectors that control the expression of a dominant negative and normally functioning MMR gene can also be used according to the invention. DNA stability can be restored using the inducible regulation, once a host cell or organism exhibiting a new output trait, altered gene, RNA or polypeptide has been generated via trait selection with or without the combination of mutagens. Restoration of functional MMR establishes a genetically stable cell or organism. In the case of MMR defective cells as a result of ectopically expressing a dominant negative MMR gene allele, the

L6: Entry 5 of 12 File: PGPB Jul 31, 2003

PGPUB-DOCUMENT-NUMBER: 20030143682
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030143682 A1

TITLE: Antibodies and methods for generating genetically altered antibodies with high affinity

PUBLICATION-DATE: July 31, 2003

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/69.1; 435/320.1, 435/326, 530/387.1, 536/23.53

CLAIMS:

We claim:

1. A method of increasing affinity of a monoclonal antibody for an antigen comprising substituting an amino acid within the variable domain of the heavy or light chain of said monoclonal antibody with a second amino acid having a non-polar side chain, whereby said affinity of said monoclonal antibody for said antigen is increased.

2. The method of claim 1 wherein said second amino acid is a proline.

3. The method of claim 2 wherein said amino acid within the variable domain of the heavy or light chain of said monoclonal antibody is an amino acid having a non-polar side chain.

4. The method of claim 3 wherein said amino acid is an alanine, or leucine.

5. The method of claim 3 wherein said amino acid is in the first framework region of the heavy chain of said monoclonal antibody.

6. The method of claim 3 wherein said amino acid is in the second framework region of the light chain of said monoclonal antibody.

7. The method of claim 2 wherein said amino acid is in position 6 of the first framework region as shown in SEQ ID NO: 18.

8. The method of claim 2 wherein said amino acid is in position 22 of the second framework region of the light chain variable domain as shown in SEQ ID NO: 21.

9. A method of increasing affinity of a monoclonal antibody for an antigen comprising substituting an amino acid within the variable domain of the heavy or light chain of said monoclonal antibody wherein said amino acid comprises a non-polar side chain, with a proline, whereby said affinity of said monoclonal antibody for said antigen is increased.

10. The method of claim 9 wherein said amino acid is an alanine, or leucine.

11. The method of claim 9 wherein said amino acid is in the first framework region of the heavy chain of said monoclonal antibody.

12. The method of claim 9 wherein said amino acid is in the second framework region of the light chain of said monoclonal antibody.

13. The method of claim 10 wherein said amino acid is in position 6 of the first framework region as shown in SEQ ID NO: 18.

14. The method of claim 10 wherein said amino acid is in position 22 of the second framework region of the light chain variable domain as shown in SEQ ID NO: 21.

15. A monoclonal antibody produced by the method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14.

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L6: Entry 10 of 12 File: PGPB May 9, 2002

PGPUB-DOCUMENT-NUMBER: 20020055106
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020055106 A1

TITLE: Method for generating hypermutable organisms

PUBLICATION-DATE: May 9, 2002

INVENTOR-INFORMATION:

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US-CL-CURRENT: 435/6; 435/325, 435/455, 435/91.1

CLAIMS:

We claim:

1. A method for generating a mutation in a gene of interest comprising the steps of: growing a hypermutable mammalian cell comprising the gene of interest and a dominant negative allele of a mismatch repair gene under control of an inducible transcriptional regulatory element; testing the cell to determine whether the gene of interest harbors a mutation; and restoring mismatch repair activity to the cell by decreasing expression of the dominant negative allele.

2. The method of claim 1 wherein the step of testing comprises analyzing a nucleotide sequence of the gene of interest.

3. The method of claim 1 wherein the step of testing comprises analyzing mRNA transcribed from the gene of interest.

4. The method of claim 1 wherein the step of testing comprises analyzing a protein encoded by the gene of interest.

5. The method of claim 1 wherein the step of testing comprises analyzing the phenotype of the cell.

6. The method of claim 1 wherein the mammalian cell is made by the process of introducing a polynucleotide comprising a dominant negative allele of a mismatch repair gene into a mammalian cell, whereby the cell becomes hypermutable.

7. The method of claim 6 wherein a reporter gene interrupted with a

polymononucleotide tract which causes a reading frame-shift is introduced into the mammalian cell to permit the monitoring of hypermutability.

8. A method for generating a mutation in a mammal comprising the steps of: growing under inducing conditions one or more mammals comprising a dominant negative allele of a mismatch repair gene under control of an inducible transcriptional regulatory element; selecting one or more mammals with a new trait acquired during the step of growing; restoring genetic stability to the mammal by subjecting the mammal to non-inducing conditions.

9. The method of claim 8 wherein the new trait is identified by analyzing a nucleotide sequence.

10. The method of claim 8 wherein the new trait is identified by analyzing mRNA.

11. The method of claim 8 wherein the new trait is identified by analyzing a protein.

12. The method of claim 8 wherein the new trait is identified by analyzing a phenotype.

13. A transgenic mammal made by the method of claim 8.

14. The transgenic mammal of claim 13 wherein the mismatch repair gene is PMS2.

15. The transgenic mammal of claim 13 wherein the mismatch repair gene is human PMS2.

16. The transgenic mammal of claim 13 wherein the allele comprises a truncation mutation.

17. The transgenic mammal of claim 15 wherein the allele comprises a truncation mutation at codon 134.

18. The transgenic mammal of claim 17 wherein the truncation mutation is a thymidine at nucleotide 424 of wild-type PMS2.

19. A method for generating a mutation in a gene of interest, comprising the steps of: growing under inducing conditions mammalian cells comprising (a) a gene of interest and (b) a dominant negative allele of a mismatch repair gene under control of an inducible regulatory element; contacting the cells with a mutagen; selecting one or more cells which comprise an altered gene, an altered RNA, an altered polypeptide, or altered phenotypic trait.

20. The method of claim 19 further comprising the step of: decreasing expression of the dominant negative allele in the selected one or more cells by culturing in non-inducing conditions.

21. The method of claim 19 wherein expression of the dominant negative allele is decreased by site directed mutagenesis of the dominant negative allele.

22. A method for generating a mutation in a gene of interest comprising the steps of: treating cells comprising (a) a gene of interest and (b) a genetic defect in a mismatch repair gene with a mutagen; selecting one or more cells which comprise an altered gene, RNA, polypeptide or phenotypic trait.

23. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in PMS2.

24. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in PMS 1.

25. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in MLH1.

26. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in MSH2.

27. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in GTBP/MSH6.

28. The method of claim 22 wherein the genetic defect in the mismatch repair gene is in MSH3.

29. The method of claim 22 wherein the genetic defect is a dominant-negative mutation.

30. The method of claim 23 wherein the genetic defect is a dominant-negative mutation.

31. The method of claim 22 further comprising the step of: introducing a complementing mismatch repair gene into the one or more selected cells whereby genetic stability is restored.

32. The method of claim 31 where the complementing mismatch repair gene is constitutively active in the one or more selected cells.

33. The method of claim 31 wherein the complementing mismatch repair gene is inducibly regulated.

34. The method of claim 31 wherein the complementing mismatch repair gene is in PMS2.

35. The method of claim 31 wherein the complementing mismatch repair gene is PMS1.

36. The method of claim 31 wherein the complementing mismatch repair gene is MLH 1.

37. The method of claim 31 wherein the complementing mismatch repair gene is MSH2.

38. The method of claim 31 wherein the complementing mismatch repair gene is GTBP/MSH6.

39. The method of claim 31 wherein the complementing mismatch repair gene is MSH3.

40. The method of claim 31 wherein the complementing mismatch repair gene is introduced into the one or more selected cells by cell-cell fusion with a mismatch repair proficient cell.

41. A method for measuring mismatch repair activity of a cell comprising the step of: assaying function of a gene in a cell wherein the gene comprises a polymononucleotide tract in its coding region which disrupts reading frame of the